

The effect of serum Magnesium levels on prognosis and mortality in patients with spontaneous intracranial hemorrhage

Serum Mg level in patients with intracranial hemorrhage

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Abstract

Aim: Non-traumatic intracranial hemorrhages are subarachnoid (SAH), intracerebral (ICH) and subdural (SH) events with a high risk of mortality and morbidity. Magnesium (Mg) plays neuroprotective and coagulation cascade roles. We tested the relationship between serum Mg levels at admission and severity scores and mortality in intracranial hemorrhages.

Material and Methods: Demographic, clinical, laboratory, and radiographic data were analyzed in this single-center prospective observational study. SAH patients were classified as mFisher score ≥ 3 and mFisher score ≤ 2 , and ICH and SH patients were classified as ICHscore ≥ 3 and ICHscore ≤ 2 . Blood Mg levels, severity scores and mortality were compared.

Results: One hundred ninety-five patients were enrolled, of which 35.4% were women and 64.6% were men. The median age was 70 years in ICH patients, 55 in SAH patients, and 68 in SH patients. Mg levels in cases with ICH score ≤ 2 were statistically significantly higher than in those with ICH score ≥ 3 ($p < 0.05$). In the SAH group, Mg values in cases with mFisher scores ≤ 2 were statistically significantly higher than those in cases with mFisher scores ≥ 3 ($p < 0.05$).

ROC analysis was applied to determine Mg values identifying exitus patients. At a cut-off value of 1.83 (AUC: 0.775), the sensitivity was 89.87% (95%CI 81-95.5) and the specificity 58.62% (95%CI 49.1-67.7) ($p < 0.05$).

Discussion: Mg levels at admission time are associated with severity scores and mortality in patients with intracranial hemorrhages.

Keywords

Emergency; Intracerebral hemorrhage; Subarachnoid hemorrhage; Subdural hemorrhage; Magnesium

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Introduction

Non-traumatic intracranial hemorrhages are subarachnoid, intraparenchymal and subdural events with a severe risk of mortality and morbidity [1]. Spontaneous intracerebral hemorrhage is responsible for 10-30% of acute cerebrovascular diseases. It is the most fatal form of stroke, affecting more than 1 million people worldwide. The most important factor determining 30-day mortality is hematoma volume and expansion [2-4].

Subarachnoid hemorrhage (SAH) refers to bleeding between the pia mater and the arachnoid mater and constitutes approximately 5% of all stroke cases [5]. It frequently occurs as a result of intracranial aneurysm rupture. SAH is more common in women over 50, and one-month mortality rate is 45% [6]. Cerebral arterial vasospasm is the most important complication of SAH. Blood flow to the arteries decreases as a result of cerebral arterial vasospasm, leading to delayed cerebral ischemia (DCI). Delayed cerebral ischemic infarction (DCII) can even occur due to DCI. DCI is also responsible for mortality and morbidity in SAH patients [7, 8].

Subdural hemorrhage (SH) refers to bleeding into the space between the dura mater and subarachnoid mater. Since it frequently occurs as a result of trauma, it is seen in only approximately 5% of all strokes. Spontaneous SH generally occurs in elderly patients due to cortical artery hemorrhage, vascular anomalies, coagulopathy, malignancy, arachnoid cyst, and cocaine use. Diagnosis may be delayed since it is not immediately suspected in patients with no history of trauma, and the prognosis is, therefore, poor [9].

Magnesium (Mg) is an intracellular cation, 60% of which is stored in bone, with important physiological functions. It prevents the release of catecholamines by inhibiting N-methyl-D-aspartate glutamate (NMDA) receptors in the central nervous system. Thus, it produces dilatation in the cerebral arteries [6, 10]. It also produces activation of factor X in the coagulation cascade through the mediation of factor VII. The resulting structural changes in factor X trigger platelet activation. Levels of the antithrombotic proteins S and C decrease. Thus, Mg exhibits a hemostatic effect [11].

The purpose of this study was to investigate the value of blood Mg levels at the time of presentation in determining the severity of hemorrhage and 30-day mortality in patients with SAH, ICH, and spontaneous SH.

Material and Methods

Patient selection

This prospective study involved patients presenting to a tertiary emergency department with SAH, ICH, and/or SH determined at cerebral tomography (CT) performed due to clinical suspicion following physical examination and evaluations, and confirmed either verbally or in writing by a specialist radiologist. The study commenced with patients capable of giving consent after receipt of the approval of the ethics committee (17.05.2018 no:61). All stages of the study were performed in compliance with the Declaration of Helsinki.

After obtaining ethical approval, five hundred eighty-five patients who presented to our hospital emergency department due to spontaneous intracranial hemorrhage within a one-year

period (20.05.2018-20.05.2019) were included in the study. Patients with a history or findings of trauma, pregnant women, those using anticoagulant medication and patients with a history or findings of malignancy were excluded. Patients aged over the age of 18 who were capable of giving consent were included. Due to the prospective nature of the study, the study included patients personally encountered by the principal and other authors and whose examination and tests were followed-up under their supervision. Patients from whom consent could not be obtained were excluded.

Data collection

Patients' age, sex, Glasgow coma scale scores and blood pressure were recorded on a specially produced form. Laboratory parameters studied from blood specimens, such as Mg levels, platelet count and international normalized ratio (INR) values were recorded from the computer database system.

ICH volume, a parameter required in order to calculate the intracerebral hemorrhage score in patients with ICH and SH identified at tomography, was calculated by a specialist radiologist using the ABC/2 formula.

Volume of Hemorrhage = $A \times B \times C \times \text{Slices/Hemorrhage Shape}$.
 A = Largest diameter of the hemorrhage on CT, B = Largest diameter 90° to A on the same CT slice, C = Number of CT slices on which hemorrhage is visible multiplied by the slice thickness (Slice with $\geq 75\%$ Area of Hemorrhage: Counts as 1 slice; Slice with 25-75% Area of Hemorrhage: Counts as 0.5 slices; Slice with $< 25\%$ Area of Hemorrhage: Counts as 0 slices), hemorrhage shape = If Round/Ellipsoid: 2; Otherwise: 3. This is a recognized scoring system used in estimating the severity of disease and 30-day survival in patients with ICH and SH. ICH ≥ 3 indicates an increased risk of mortality (26% in ICH ≤ 2 , but 74% in ICH ≥ 3) [12]. Patients were therefore classified as ICH score ≤ 2 and ICH score ≥ 3 .

Modified Fisher (mFisher) scores of SAH cases were also calculated by a specialist radiologist. Grade 1=focal or diffuse, thin SAH, no IVH, Grade 2= focal or diffuse, thin SAH, with IVH, Grade 3 = focal or diffuse, thick SAH, no IVH, Grade 4 = focal or diffuse, thick, SAH, with IVH. The mFisher scale is a risk classification showing vasospasm in SAH. The risk of vasospasm development is 6% in mFisher 1, 15% in mFisher 2, 35% in mFisher 3, and 34% in mFisher 4 [13,14]. Patients were therefore classified as mFisher ≥ 3 and mFisher ≤ 2 . The Mg levels in the groups were subjected to comparative analysis. Patients were also followed up for a 30-day mortality rate.

Statistical Analysis

Statistical analysis was performed on IBM SPSS Statistics Version 24 software. Descriptive data were summarized as patient number (n) and %. Pearson's chi-square and Fisher's exact tests, and chi-square trend analyses were used to compare categorical data between groups. The normality of the distribution of continuous data was evaluated using the Kolmogorov-Smirnov test. The data were found not to exhibit normal distribution ($p < 0.05$). Continuous data were expressed as median (IQR) values. The Mann Whitney U test was therefore applied to compare data between the two groups, and the Kruskal-Wallis H test (post hoc Bonferroni corrected Mann-Whitney U test) was used to compare data between more than two groups. The relationship between ICH and mFisher

scores and laboratory values were analyzed using Spearman's correlation analysis, and ROC analysis was performed to calculate optimal cut-off values for laboratory findings. P values <0.05 were considered statistically significant.

Results

Women constituted 35.4% of the 195 patients enrolled, and men 64.6%. The mean age was 70 years in ICH patients (16), 55 in SAH (23.5) and 68 in SH (21). Mg levels from laboratory values by type of hemorrhage were 1.77 mg/dl for ICH (0.35), 1.77 mg/dl for SAH (0.27), and 1.73 mg/dl for SH (0.25) (Table 1). Mann Whitney U analysis applied to ICH and SH group cases revealed that Mg levels in cases with ICH scores ≤2 were statistically significantly higher than in those with ICH scores ≥3 (p<0.05). In the SAH group cases, Mg values in cases with Fisher scores ≤2 were statistically significantly higher than those in cases with Fisher scores ≥3 (p<0.05) (Table 2).

The mortality from all hemorrhages was 40.5%. The highest mortality rate, at 44.7%, was determined in ICH. Examination of mean age and clinical characteristics, mFisher, and ICH scores by exitus status revealed a statistically significant difference in mortality between the groups based on ICH score grouping (p<0.05). The age and INR values were significantly lower in surviving cases than in fatal cases (p<0.05). Mg and platelet values were significantly higher in surviving cases than in fatal cases (p<0.05), while hematoma volume was lower. No statistically significant difference was observed in terms of other variables (Table 3). Multivariate logistic regression analysis was applied to identify independent factors predicting mortality. Age, Mg, ICH score, platelet count, hematoma volume and INR emerged as independent risk factors in determining mortality (p<0.05).

ROC analysis was applied to determine Mg values in identifying exitus patients. At the cut-off value of 1.83 mg/dl (AUC: 0.775), sensitivity was 89.87% (95%CI 81-95.5), the specificity was 58.62% (95%CI 49.1-67.7) (p<0.05). (Figure 1).

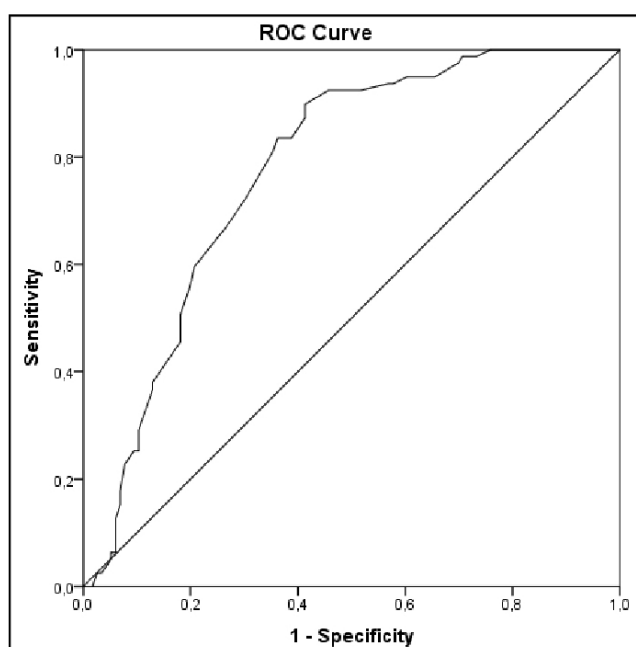


Figure 1. Receiver Operating Characteristic (ROC) curve of magnesium level in predicting mortality

Table 1. Distribution of continuous and ordinal variables according to patient groups

	ICH Median (IQR)	SAH Median (IQR)	SH Median (IQR)
Age/year	70 (16)	55 (23,5)	68 (21)
Admission GKS	15 (6,25)	15 (2)	15 (4,5)
Hematoma volume (cm ³)	4,05 (17,63)		30,1 (43)
Platelets (10 ⁹ /L)	219,5 (110)	233,5 (96,5)	227 (80,5)
Magnesium (mg/dl)	1,77 (0,35)	1,77 (0,27)	1,73 (0,25)
INR	1,11 (0,22)	1,09 (0,15)	1,11 (0,17)

GCS: Glasgow coma scale, INR: International normalized ratio.

Table 2. Distribution of Magnesium values in comparison with intracranial hemorrhage score (ICH) and mFisher scores

	Magnesium (mg/dl)		Z	p	
	Median	IQR			
ICH score					
ICH cases	≤2	1,87	0,33	-5,053	0,000
	≥3	1,67	0,25		
SUBDURAL cases	≤2	1,76	0,21	-2,184	0,029
	≥3	1,63	0,07		
mFisher					
SAH cases	≤2	1,94	0,28	-2,894	0,004
	≥3	1,74	0,27		

ICH: intracerebral hemorrhage, SH: subdural hemorrhage, SAH: subarachnoid hemorrhage

Table 3. Relationship between mortality and intracranial hemorrhage score (ICH score), mFisher score, continuous and ordinal variables

	live	ex	X ²	p		
mFisher						
≤2	7	87,5	1	12,5	2,191	0,236
≥3	29	60,4	19	39,6		
ICH score						
≤2	71	78	20	22	45,191	0,000
≥3	9	18,8	39	81,3		
	Median (IQR)	Median (IQR)	Z	p		
Age/year	69 (19,5)	74 (16)	-4,407	0,000		
Magnesium (mg/dl)	1,9 (0,34)	1,7 (0,17)	-6,517	0,000		
Platelet (10 ⁹ /L)	242,5 (90)	202 (131)	-2,615	0,009		
Hematoma volume (cm ³)	2,75 (12,45)	16,8 (28)	-4,158	0,000		
INR	1,11 (0,17)	1,11 (0,49)	-3,332	0,001		
Sistolic blood pressure (mmHg)	150,5 (48)	157 (76)	-0,047	0,963		
Diastolic blood pressure (mmHg)	80 (28,75)	80 (28)	-0,444	0,657		

ICH score: intracranial hemorrhage score, INR: international normalized ratio

Discussion

The basic pathology in SAH, which is especially important among intracranial hemorrhages, since it particularly affects the young population, involves the impairment of cerebral circulation due to intracranial pressure increasing under the effect of the hemorrhage. The resulting DCI determines the course of the disease. The prevention of DCI will also improve the prognosis. Due to its cerebral vasodilatation and neuroprotective effects, the role and effects of Mg in intracranial hemorrhages have

been investigated in several studies.

Can et al. reported that Mg levels during the follow-up of patients with cerebral aneurysms differed from levels at the time the hemorrhage (SAH) developed. However, the levels the day prior to rupture were the same. The authors concluded that Mg does not play any role in aneurysm rupture, but that blood levels decrease in patients with developing SAH [15]. However, that study did not investigate the effect of this decrease in Mg levels on prognosis. We investigated the relationship between Mg values at time of presentation and mFisher scores. SAH was identified in 57 of the 195 patients enrolled in this study. Mg levels were significantly higher in patients with mFisher scores ≥ 3 . A decrease in Mg values had an adverse impact on prognosis. Liotta et al examined the relationship between hemorrhage thickness and Mg levels in SAH. They observed that every 1 mg/dl increase in blood Mg values reduced the severity of hemorrhage. Since SAH patients with hemorrhage exceeding 1 mm in size were classified as mFisher 3 and 4, they reported that low Mg levels were indirectly related to prognosis [16]. However, they did not compare variations in Mg levels and mFisher scores. Ours is the first study to compare Mg levels and mFisher scores. An increased mFisher score is an important marker of intracranial vasoconstriction and therefore of DCI. We predict that a decrease in Mg levels worsens the prognosis. In addition, IMASH, MASH II and Sommer et al. investigated the effects of Mg therapy on neurological outcomes in SAH patients. They applied varying doses of Mg, and no difference was observed in neurological outcomes compared with placebo [17-19]. However, treatment was not planned based on Mg levels and severity scores at the time of admission. The relationship between Mg levels and prognosis could not therefore be clearly established. We evaluated patient prognosis in terms of Mg levels and mFisher scores, and observed that a decrease in Mg levels affected prognosis. We, therefore, think that treatment should be planned based on Mg levels in the period between the onset of hemorrhage and the occurrence of DCI.

ICH score is used to estimate the severity of disease in ICH patients. Behrouz et al. reported that Mg values at the time of presentation of 1.7 mg/dl or below were correlated with ICH scores ≥ 3 [2]. We also found that Mg values were statistically significant in ICH patients at time of admission ICH scores ≥ 3 . Liotta et al. compared hematoma volume and changes in Mg levels at time of presentation and after 24 hours in ICH patients. A large hematoma volume was determined in patients with low Mg levels on arrival. That study also investigated patients' three-month outcomes and observed correlations between hematoma expansion and Mg levels, also between functional outcomes [20]. Similarly, Goyal et al. reported lower ICH Score and hematoma volume in ICH patients with high Mg levels at the time of admission, and reported that Mg level on admission was an important factor [6]. The essential parameter in both scoring systems determining disease severity is hematoma volume. Liotta et al. found an inverse correlation between Mg levels and the size of hemorrhage in SAH, while Goyal et al. identified Mg levels as an independent risk factor affecting hematoma volume [6, 16]. Our results are consistent with these findings, showing that Mg levels at time of admission are associated with the severity of disease for both SAH and

ICH patients.

Twenty-five cases in the present study were diagnosed as spontaneous SH. The only research of the effects of Mg therapy in SH in the literature was Heat et al.'s study involving experimentally induced traumatic SH in mice receiving i.v. Mg and saline solution as placebo. Mg was described as a factor exacerbating neurological status in the presence of SH [9]. However, Heat et al.'s study involved traumatic animals. In the present study, we determined a statistically significant but poor relationship between ICH score and Mg levels. Further studies with larger patient numbers are now required for SH patients. The effect of Mg on mortality was only investigated in the IMASH study; the mortality rate in SAH patients given Mg was 10%, compared to 12% in the placebo group [17]. In our study, mortality rates also increased in cases with Mg values less than 1.83 mg/dl among our entire patient group (ICH, SAH, and SH). When the effect of other variables on mortality was examined, we found that mortality increased with hematoma volume, INR, ICH score and age, and as platelet counts decreased. The administration of platelets to patients with thrombocytopenia, and of cofactor or TDP to patients with high INR is recommended in the approach to intracranial hemorrhages. However, the role of Mg in the treatment of intracranial hemorrhages is still unclear.

There are a number of limitations to this study. Since the patient group consisted of individuals with intracranial hemorrhage, who were largely unconscious, obtaining consent from these was problematic. Patients whose relatives' consent was received were included in the study. Therefore, the number of our patients was low.

Conclusion

Non-traumatic intracranial hemorrhages involve a high risk of mortality and morbidity. Mg levels at the time of presentation are associated with mortality independently of scoring systems employed to predict prognosis. Determining the role of Mg in hemorrhage control through further studies with larger patient numbers will make a major contribution to emergency approach.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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